PREDICTIVE DETERMINANTS FOR GASTRO-OESOPHAGEAL MALIGNANCY IN DYSPEPTIC PATIENTS WITH ALARM FEATURES

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CERTIFICATE

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This is to certify that the dissertation **" PREDICTIVE DETERMINANTS FOR GASTRO-OESOPHAGEAL MALIGNANCY IN DYSPEPTIC PATIENTS WITH ALARM FEATURES"** is the bonafide original work of **Dr.S.CHANDRA MOHAN** in partial fulfillment of the requirements for **D.M (GASTROENTEROLOGY)**

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CONTENTS

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INTRODUCTION

Dyspepsia is a nonspecific term to denote upper abdominal discomfort that is thought to arise from the upper-GI tract.[1,2] Dyspepsia may encompass a variety of more specific symptoms, including epigastric discomfort,bloating, anorexia, early satiety, belching or regurgitation, nausea, and heartburn.

Symptoms of dyspepsia most commonly result from 1 of 4 underlying disorders: peptic ulcer disease, GERD, functional disorders (nonulcer dyspepsia),and malignancy: malignancy is present in 1% to 3% of patients with dyspepsia and peptic ulcer disease in another 5% to 15%.[3-6]

The estimated annual prevalence in western countries is approximately 25% to 40% accounting 2-5% of all primary care consultations.[7] In India almost one-third of the population has symptoms.[8]

Endoscopy is the procedure of choice for the diagnostic evaluation of this common, longterm, symptom shifting, expensive disorder.It offers the potential for early diagnosis of structural disease.Yet, given the large numbers of patients with dyspepsia, it is not practical to perform endoscopy in all patients with dyspepsia.

Age and alarm features have been used in an attempt to identify those patients with dyspepsia who harbor structural disease.

Patients with a new onset of dyspepsia after 45 to 55 years of age and those with symptoms or signs (unintended weight loss, Upper Gastrointestinal bleeding or iron deficiency anemia, progressive dysphagia, persistent vomiting, palpable mass, lymphadenopathy, jaundice) that suggest structural disease are advised to undergo initial endoscopy.[3]

Patients with alarm features and dyspepsia have significantly worse outcomes than the population at large.

In a prospective questionnaire study, patients with alarm symptoms and dyspepsia had a

significant increase in both GI cancer and mortality over a 3-year period.[9]Even though alarm features predict relatively poor patient outcomes, they have a low predictive value for GI cancer.

In a meta-analysis of 15 studies that evaluated more than 57,000 patients with dyspepsia, alarm symptoms showed a positive predictive value for GI cancer

of <11% in all but 1 of these studies.[5] The negative predictive value of alarm symptoms was much higher, at > 97%, because of the low prevalence of GI cancer in that population.

A second meta-analysis of 26 studies that totaled more than 16,000 patients with dyspepsia showed similar results: the positive predictive value of alarm symptoms for upper-GI cancer was only 5.9% and the negative predictive value

was >99%.[6]

Unfortunately, clinical impression, demographics,risk factors, history items, and symptoms also do not adequately distinguish structural disease from functional disease in patients with dyspepsia who are referred for endoscopy.[10] It is worth noting that one fourth of patients with malignancy and dyspepsia have no alarm symptoms.[6]

AIM OF THE STUDY

1.To determine the predictive factors of gastroesophageal malignancy in dyspeptic patients presenting with alarm features.

2.To arrive at or to refine indications for Upper Gastrointestinal Endoscopy in patients with dyspepsia.

REVIEW OF LITERATURE

DEFINITIONS

Dyspepsia is defined as chronic or recurrent pain or discomfort centered in the upper abdomen. Discomfort is defined as a subjective negative feeling that is nonpainful, and can incorporate a variety of symptoms including early satiety or upper abdominal fullness. Patients presenting with predominant or frequent (more than once a week) heartburn or acid regurgitation should be considered to have gastroesophageal reflux disease (GERD) until proven otherwise **– ACG 2005**.[11]

NICE Guidelines (2004)[12]

Dyspepsia in unselected patients in primary care is defined broadly to include patients with recurrent epigastric pain, heartburn or acid regurgitation with or without bloating, nausea or vomiting.

The broad definition of dyspepsia has complicated research efforts and limited the value of research observations to clinical practice. In response, some investigators have attempted to clarify the definition of dyspepsia by using defined criteria, for example ROME criteria.

The Rome committees serve as the nidus to modify and update information on these disorders for research and patient care. By necessity, the group develops criteria by consensus (via the "Delphi Approach") and the process has matured through three generations, producing a series of publications (Rome I, II and III), with an increased evidence-based approach to the recommendations.

ROME III(2006) criteria[13] defines dyspepsia in functional gastroduodenal disorders.

Functional Gastroduodenal Disorders are classified into

B. Functional gastroduodenal disorders

B1. Functional dyspepsia

B1a. Postprandial distress syndrome

B1b. Epigastric pain syndrome

B2. Belching disorders

B2a. Aerophagia

B2b. Unspecified excessive belching

B3. Nausea and vomiting disorders

B3a. Chronic idiopathic nausea

B3b. Functional vomiting

B3c. Cyclic vomiting syndrome

B4. Rumination syndrome in adults

B1. Diagnostic Criteria* for Functional Dyspepsia

1. One or more of:

a. Bothersome postprandial fullness

b. Early satiation

c. Epigastric pain

d. Epigastric burning

AND

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

B1a. Diagnostic Criteria* for Postprandial Distress Syndrome

Must include one or both of the following:

1. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week.

2. Early satiation that prevents finishing a regular meal, at least several times per week.

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis*

Supportive criteria

1. Upper abdominal bloating or postprandial nausea or excessive belching can be present

2. EPS may coexist

1b. Diagnostic Criteria* for Epigastric Pain Syndrome

Must include *all* of the following:

1. Pain or burning localized to the epigastrium of at least moderate severity at least once per week.

2. The pain is intermittent.

3. Not generalized or localized to other abdominal or chest regions.

4. Not relieved by defecation or passage of flatus.

5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders.

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.*

Supportive criteria

1. The pain may be of a burning quality but without a retrosternal component.

2. The pain is commonly induced or relieved by ingestion of a meal but may occur while Fasting.

3. Postprandial distress syndrome may coexist.

The ROME committee proposed to define Functional dyspepsia at 2 levels.

A general, more umbrella definition of Functional dyspepsia , to be used mainly for clinical purposes, and although further research on more specific definitions is ongoing, is provided under category B1.

However, particularly for pathophysiological and therapeutic research purposes, newly defined entities of

(1) meal-induced dyspeptic symptoms (PDS, defined under category B1a)

and

(2) epigastric pain (EPS, defined under category B1b), used operatively.

DYSPEPTIC SYMPTOMS AND THEIR DEFINITIONS:

Epigastric pain

Epigastric refers to the region between the umbilicus and lower end of the sternum, and marked by the midclavicular lines. Pain refers to a subjective, unpleasant sensation; some patients may feel that tissue damage is occurring. Other symptoms may be extremely bothersome without being interpreted by the patient as pain.

Epigastric burning

Epigastric refers to the region between the umbilicus and lower end of the sternum, and marked by the midclavicular lines. Burning refers to an unpleasant subjective sensation of heat.

Postprandial fullness

An unpleasant sensation like the prolonged persistence of food in the stomach.

Early satiation

A feeling that the stomach is overfilled soon after starting to eat, out of proportion to the size of the meal being eaten, so that the meal cannot be finished. Previously, the term "early satiety" was used, but satiation is the correct term for the disappearance of the sensation of appetite during food ingestion.

Uninvestigated versus investigated dyspepsia

It is important to distinguish the subjects with dyspeptic symptoms who have not been investigated from patients with a diagnostic label after investigation, with or without an identified causal abnormality.

Organic versus idiopathic dyspepsia

From an etiological viewpoint, patients with dyspeptic symptoms can be subdivided into 2 main categories:

1. Those with an identified organic or metabolic cause for the symptoms where, if the disease improves or is eliminated, symptoms also improve or resolve (eg, peptic ulcer disease, GERD with or without esophagitis, malignancy, pancreaticobiliary disease, or medication use).

2. Those with no identifiable explanation for the symptoms.In some of these patients, an identifiable pathophysiological or microbiologic abnormality of uncertain clinical relevance (eg, *Helicobacter pylori* gastritis) may be present, which is not thought to explain the symptoms. Others have abnormal motor or sensory dysfunction

(eg, altered gastric emptying, fundic dysaccommodation, or gastroduodenal hypersensitivity) of uncertain significance. This broad group of patients with idiopathic dyspepsia has previously been referred to as nonulcer dyspepsia, essential dyspepsia, idiopathic dyspepsia, or functional dyspepsia.

EPIDEMIOLOGY

Approximately 20% to 30% of people in the community each year report chronic or recurrent dyspeptic symptoms.[14,15] Although these data represent uninvestigated dyspepsia and often also included heartburn, an organic cause is found in only a minority of dyspeptic subjects who are investigated, and hence it is reasonable to assume that the majority would have functional dyspepsia.[16,17]

Based on prospective studies of subjects who report dyspeptic symptoms for the first time, the incidence is approximately 1% per year.[18] The majority of patients with unexplained dyspeptic symptoms continue to be symptomatic over the long-term despite periods of remission.[19] Approximately, 1 in 2 subjects is estimated to seek health care for their dyspeptic symptoms at some time in their life.[20] Pain severity and anxiety (including fear of serious disease) appear to be factors associated with consulting behavior.[20,21]

HETEROGENEITY OF FUNCTIONAL SYMPTOMS: SUBGROUPS

It seems likely that chronic unexplained dyspepsia includes different types of patients with distinct underlying pathophysiologies who require different management approaches.[22] However, it has been particularly difficult to identify these subgroups reliably. Subclasses based on symptom clusters have been proposed. In clinical practice, however, this classification showed great overlap between subclasses, limiting its value. Identifying the predominant symptom was shown to distinguish subgroups with different demographic and symptomatic properties and with some relationship to putative pathophysiological mechanisms like delayed gastric emptying and presence of *H pylori*.[23] Thus, the Rome II committee proposed a subdivision according to the predominant symptom being pain or discomfort, but this subdivision

has also been criticized because of the difficulty distinguishing pain from discomfort, the lack of an accepted definition of the term predominant, number of patients who do not fit into one of the subgroups, and especially the lack of stability, even over short time periods.[24,25]

A different approach was based on attempts to identify pathophysiology-based subgroups. Thus, associations were shown between symptom patterns and delayed gastricemptying,[26,27] impaired fundic accommodation,[28] and visceral hypersensitivity.[29] However, the association of these pathophysiological mechanisms with symptoms has not been confirmed in other studies.[30-32]

PATHOPHYSIOLOGICAL DISTURBANCES IN FUNCTIONAL DYSPEPSIA

Approximately 40% of patients with functional dyspepsia have delayed gastric emptying[31.] Stanghellini *et al.* in 343 Italian patients reported that delayed gastric emptying was significantly more frequent in patients characterized by female sex, low body weight, presence of relevant and severe postprandial fullness, nausea,vomiting, and absence of severe epigastric pain; female sex,relevant and severe postprandial fullness, and severe vomiting were independently associated with delayed gastric emptying of solids.[34]

In a separate study of 483 patients, the same Italian group identified distinct subgroups based on predominant symptoms and gastric emptying; one was characterized by predominant epigastric pain, male gender and normal gastric emptying, and a second by predominant nonpainful symptoms, female gender, and a high frequency of associated irritable bowel syndrome and delayed gastric emptying.[23]

Sarnelli *et al.* also reported that delayed gastric emptying was associated with postprandial fullness and vomiting.[27] Other studies, however, have failed to identify a definite symptom profile associated with delayed gastric emptying suggesting there is not a simple association.

There is evidence that the stomach and other regions of the gut including the duodenum and esophagus are hypersensitive to distention in functional dyspepsia, although this applies only in a

subgroup[35-38].

Tack *et al.* recently reported in 160 patients with functional dyspepsia that one third had gastric hypersensitivity and this abnormality was associated with increased postprandial pain as well as belching and weight loss.[29]

In a barostat study, Tack *et al.* studied patients with functional dyspepsia; impaired gastric accommodation to a meal (a "stiff fundus") was found in 40%, and this abnormality was associated with early satiety and weight loss but not with hypersensitivity to gastric distention, presence of *H. pylori*, or delayed gastric emptying.[29]However, Boeckxstaens *et al.* failed to replicate these findings; while postprandial symptoms were more often evoked with a meal in functional dyspepsia, there was no clear symptom profile that was associated with a failure of fundic relaxation.[30]

Noninvasive testing is available to assess abnormal fundic accommodation including gastric ultrasound, SPECT, and MRI, but the clinical relevance of identifying this abnormality remains in some dispute in terms of defining therapeutic interventions.[39]

New clinical tests of gastric function are under evaluation. The water-load test and nutrient-load test may help identify gastric dysfunction in clinical practice. Currently, patients with gastroduodenal motility disturbances,gastroduodenal hypersensitivity, or other pathophysiological abnormalities of uncertain relevance are not excluded from the functional dyspepsia umbrella.

ALARM FEATURES AND IDENTIFICATION OF STRUCTURAL DISEASE IN UNINVESTIGATED DYSPEPSIA

New-onset dyspepsia in older age is an alarm feature or redflag. The American College of Physicians in 1985 published a guideline recommending that patients who were over the age of 45 deserved referral for prompt endoscopy to rule out underlying malignancy, as gastric cancer is very rare in the United States below the age of 45 yr although it increases thereafter.

Some studies have reported that older age is an independent risk factor for identifying underlying

structural abnormalities, but the results have been inconsistent.[40,41]

Recent ACG guidelines recommends prompt endoscopy for patients over the age of 55 without alarm features.[11]

The recommended age threshold for endoscopy also differs among different regions in Asia.[42,43]

In Hong Kong, 10% of patients with gastric cancer are aged less than 45 years. Sung et al reported that gastric cancer was found in three patients (0.1%), who were aged below 45 years and who did not have alarm symptoms, among 2,918 patients with dyspepsia. The investigators suggested that the "test-and-endoscope" strategy might be a more feasible approach for dyspepsia in Hong Kong.[42]

In Singapore, the relative frequency of gastric cancer was 1.15 per 1,000 upper endoscopies in patients with simple dyspepsia and aged below 45 years. An age threshold of 45 years was therefore recommended for patients withsimple dyspepsia in Singapore.[43]

A study from Taiwan considered that 40 years of age might be an appropriate age threshold for endoscopy, as 2.4 cases would be missed every year if they followed the international guidelines of 45 years.[44]

A recent prospective study in Southern India has arrived cut-off age for malignancy which was between 35 and 44 years (for females 38 years with sensitivity of 70%,specificity of 61and for males, 43.5 years with sensitivity of 88%, specificity of 62%).[45]

Several other ***alarm features*** have been traditionally applied to try and identify serious underlying disease in dyspepsia,especially malignancy.

These include

1.unexplained weight loss 2.anorexia	8.anemia 9.jaundice

3.Early satiety 4.vomiting 5.progressive dysphagia 6.odynophagia 7.bleeding	10.an abdominal mass 11.lymphadenopathy 12.family history of upper gastrointestinal tract cancer 13.history of peptic ulcer 14.previous gastric surgery or malignancy

Upper gastrointestinal malignancy is rarely present in young patients without alarm features, but the positive predictive value of alarm features remains very poor.[46,47] Many studies and meta-analysis gives variable outcomes in patients with alarm features.

Kapoor et al determined the predictive value of alarm symptoms in a cohort of 1,852 patients undergoing upper endoscopy. The mean age for cancer was 54 ± 12 years. Cancer prevalence was 8.2% and gastric ulcer prevalence was 5.3%. In the same study, the predictive value as odds ratio (OR) for dysphagia was 3.1, weight loss 2.6, and 9.5 for those aged above 55 years. All these were found to have a positive predictive value for risk of cancer.[48]

A meta-analysis which included 17 case studies and nine cohort studies showed that the pooled sensitivities of individual alarm symptoms varied from 9 to 41%, the pooled positive predictive value ranged from 4.6 to 7.9%, and was 5.9% for 'having any alarm symptom'.The pooled negative predictive value was 99.4% for'having any alarm symptom'. The analysis concluded that the risk of upper gastrointestinal malignancy in any individual without alarm symptoms is very low, but approximately one in four patients with upper gastrointestinal cancer have no alarm symptoms at the time of diagnosis.[49]

A recent Meta-analysis[6] states that alarm features have limited predictive value for an

underlying malignancy.The analysis which 15 studies evaluated a total of 57,363 patients, of whom 458 (0.8%) had cancer. The sensitivity of alarm symptoms varied from 0% to 83% with considerable heterogeneity between studies. The specificity also varied significantly from 40% to 98%. A clinical diagnosis made by a physician was very specific (range, 97%–98%) but not very sensitive (range, 11%–53%).

Sundar et al[50] in his retrospective study analysed 228 upper GI cancers and found only 14 patients (6.2%) presented without alarm symptoms. Among those with alarm features 10.9% were 55 years or younger and 0.9% were aged less than

45 years.8%of the patients with cancer under the age of 55 presented with uncomplicated dyspepsia. In patients older than 55 years, 4.4% presented with uncomplicated dyspepsia. The study identified that only a very small proportion of patients with uncomplicated dyspepsia had upper GI cancer diagnosed at a curative stage.However, limiting open access endoscopy to those with alarm symptoms would have potentially ‘‘missed’’ 14 patients, seven of whom had no evidence of metastases on imaging.

Numans et al[51] suggested thorough evaluation of 'classical' alarm symptoms in dyspeptic patients whichmight help minimize unnecessary gastroscopy requests by GPs. In this multicenter study, 861 consecutive patients were investigated with first-time gastroscopy (study population). Another 1153 patients were studied during the next 6 years (validation population). Positive answers regarding the symptoms, weight loss and dysphagia, together with negative answers on pain during the night and heartburn, predicted malignancy in the study population with an AUC (area under the curve) of 0.90. 'Alarm symptoms' performed less well in the study population (AUC 0.85), although reproducibility was better in the validation population (0.71 versus 0.63).

D. J. Bowreyet al[52] reviewed a prospectively compiled database of 4,018 subjects who underwent open access gastroscopy. Gastroscopy identified esophagogastric carcinoma in 123 (3%) of the 4,018 subjects.

Of these 123 patients, 104 (85%) with esophagogastric cancer had ‘‘alarm’’ symptoms (anemia, mass, dysphagia, weightloss, vomiting).The symptoms of the remaining 15% were those of uncomplicated ‘‘benign’’ dyspepsia. The patients with ‘‘alarm’’ symptoms had a significantly more advanced tumor stage (metastatic disease in 47% vs 11%; $p < 0.001$), were less likely to undergo surgical resection (50% vs 95%; $p<0.001$), and had a poorer survival (median, 11 vs 39 months; $p = 0.01$) than their counterparts without such symptoms.The author concluded that patients with early curable cancers often have only dyspeptic symptoms, and their diagnosis will be delayed until the symptoms of advanced cancer develop.

M B Wallace et al[53] have found that age and the presence of “high risk” symptoms are poor predictors of the presence of major endoscopic findings in the upper gastrointestinal tract. Among patients aged more than 45 or those with significant predictors,23% had a major pathological finding (positive predictive value). Among younger patients with no significant predictors, 88% had no major pathological findings (negative predictive value). For cancer alone, 3% of patients with any significant predictor (age >45, male sex, anaemia, bleeding) were found to have cancer (positive predictive value), and 99% of patients with no significant predictors had no cancer (negative predictive value).the study demonstrate the need for better clinical predictors of upper gastrointestinal pathology. In the absence of better clinical predictors, the study also demonstrates the need for less invasive and thus more widely applicable endoscopy.

A prospective database study of 5224 consecutive patients with uncomplicated dyspepsia showed 22 malignancy at endoscopy.These patients were about 20 years older than patients with no malignancy ($p< 0.001$).The Mean age of females with cancer was almost 10 years higher compared to males($p=0.002$).The age cut-offs identified were 35 years for males and 56 years for females.[54]

A long history of symptoms in patients should make cancer unlikely but a symptom duration threshold has not been defined in the literature. Use of antisecretory therapy can mask a cancer

at endoscopy but does not appear to alter the outcome .

The patient who presents with new onset dyspepsia or because of chronic symptoms needs an appropriate, evidence based clinical evaluation. The physician generally wishes to ascertain the likely cause of the symptoms and exclude underlying serious structural disease. However, the patient may actually be presenting not necessarily because of the symptoms *per se* but because of a fear of serious disease or recent psychological distress. It is reasonable that the physician identify and address such issues as fear of cancer or underlying heart disease in order to optimize management.

The patient requiring major reassurance needs to be differently managed than one who does not have such concerns, but fear of serious disease probably explains only some health care seeking behavior. The physician also needs to decide whether pharmacological therapy is required, including which drug and for how long. This in turn depends on the underlying provisional diagnosis, which may need to be refined after the patient has initially had a trial of therapy.

MANAGEMENT OPTIONS IN YOUNGER PATIENTS WITH NO ALARM FEATURES

A number of management options are available to the clinician in younger patients with no alarm features with uninvestigated dyspepsia. A wait-and-see strategy of patient reassurance and education, with use of over-the-counter antacids, H2-blockers, or PPIs and reevaluation can be considered, particularly in primary care.

Another strategy worth considering is prescription of empirical full-dose or highdose antisecretory therapy, reserving further evaluation for those who are either unresponsive or have an early symptomatic relapse after ceasing medication. Empiric antisecretory therapy was the backbone of the guideline proposed by the American College of Physicians and is still widely applied in practice .

A third approach applies *H. pylori* test and-treat as the initial strategy, currently most widely recommended around the world.[55,56] Here, young patients without alarm features are tested for

H. pylori infection. If *H. pylori* is detected, empiric antibiotic therapy is prescribed in an attempt to eradicate the infection; *H. pylori*-negative patients are treated with empiric antisecretory therapy initially.A modification of the *H. pylori* test-and-treat strategy is to either prescribe empiric antisecretory therapy first and reserve *H. pylori* testing later for failures, or apply empiric antisecretory therapy after *H. pylori* eradication fails to relieve symptoms. A final approach is to perform prompt EGD for all patients with dyspepsia. The best option remains under debate, but new data are available to help guide a rational decision.

TEST-AND-TREAT H. pylori

The rationale for noninvasive *H. pylori* testing is the identification of underlying peptic ulcer disease. For example, in Scotland where the incidence of peptic ulcer is high, McColl *et al.* showed that in patients with dyspepsia and a positive C13 urea breath test had a duodenal ulcer (DU) in 40% and gastric ulcer (GU) in 13%; those who were breath test negative had a DU in 2%andGU in 3%.[57]

Other studies suggest that between 20% and 60% of patients with dyspepsia who are *H. pylori* infected will have underlying peptic ulcer disease,but this varies widely depending upon the background incidence of peptic ulcer.

Cost-effectiveness studies in the United States suggest that when the prevalence of *H. pylori* infection in patients with functional dyspepsia is less than 12% or when the prevalence of *H. pylori* infection in patients with peptic ulcer disease is less than 48%, initial empirical treatment with a PPI is preferable[58].

Others have suggested that when *H. pylori* infection decreases below 20%, empiric PPI therapy starts to dominate test-and-treat in uninvestigated dyspepsia.[59]

ACG 2005:[11]

The application of a test-and-treat strategy for H. pylori should be based on the practice setting.

High prevalence populations in the United States (e.g., recent immigrants from developing countries) should undergo test-and-treat as the preferable nonendoscopic strategy. Conversely, in communities where gastric or esophagealcancer has a high incidence, prompt endoscopy should be considered early but this would not apply to most of the country.

In low-prevalence populations (e.g., high socioeconomic areas, where the background prevalence of ulcer or H. pylori infection is low), an alternative strategy is to prescribe first a course of antisecretory therapy empirically for 4–8 wk. If the patient fails to respond or relapses rapidly on stopping antisecretory therapy, then the test-and-treat strategy is best applied before consideration of referral for EGD. EGD is not mandatory in those who remain symptomatic as the yield is low; the decision to endoscope or not must be based on clinical judgement.

Grade of evidence for test-and-treat or acid suppression:A

Grade of evidence for a H. pylori prevalence of less than 10% in the local community as the cutoff for deciding to use empiric acid suppression rather than test-and-treat: C

Disadvantages of Test-and-Treat

A notable disadvantage of test-and-treat is that cure of *H. pylori* infection will only lead to a minority reporting symptom improvement, as demonstrated in the above management trials, and this can be confusing to the clinician.

However, endoscopy and targeted medical therapy does no better.Indeed, eradication of *H. pylori* infection does not relieve symptoms in all patients with peptic ulcer disease, with at least one third continuing to be symptomatic.[60,61]The choice of the *H. pylori* test is critical. Many serological tests have not been locally validated, and have suboptimal sensitivity and specificity in practice.[62] The urea breath test and stool antigen test are currently the most accurate noninvasive diagnostic tools and can be used with confidence.

The value of noninvasive *H. pylori* testing, even if a local evaluated test is applied, still depends on the

positive and negative predictive value, which in turn is related to the background prevalence of *H. pylori* infection. When *H. pylori* is very uncommon, a positive test is more likely to be a false positive. Where *H. pylori* infection is highly prevalent,a negative result is more likely to be a false negative . Cost-effectiveness studies suggest that the stool test and the urea breath test that detect active infection are preferable to serological tests in the United States.[63,64]

The current treatment of choice for *H. pylori* infected patients is a combination of PPI (standard dose twice daily) with amoxicillin (1 g twice daily) and clarithromycin (500mg twice daily) administered for 7–10 days (7-day therapy is approved with rabeprazole; 10-day therapy is approved with lansoprazole, omeprazole, pantoprazole, and esomeprazole). Metronidazole (400 mg twice daily) may be substituted for amoxicillin in this regimen if the patient is allergicto penicillin. An alternative strategy is the combination of Bismuth, metronidazole, and tetracycline (Bismuth subsalicylate [Pepto Bismol_] 525 mg QID + metronidazole 250mg QID + tetracycline 500 mg QID) combined with a PPI for 14 days .A final issue relates to potential complications of therapy.Antibiotic allergies and super-infection can occur.

It is controversial whether eradication of *H. pylori* infection increases the risk of development of reflux esophagitis or reflux symptoms. However, it appears likely that this risk is only present in those with a predisposition to GERD who also have severe gastritis in the body or fundus that impairs acid secretion, which is reversed with *H. pylori* eradication; this is likely to be uncommon in most of the United States. Hence, this issue while much discussed should not be a major clinical concern when contemplating test-and-treat, unless convincing data to the contrary arise. Progression of *H. pylori* gastritis may occur on acid suppression, and some have suggested *H. pylori* eradication should be considered for all patients requiring long-term acid suppression, which seems reasonable.[65,66] An unresolved issue is whether test-and-treat will widen the problem of community acquired antibiotic resistance.

PROMPT ENDOSCOPY

Advantages of Prompt Endoscopy

There is empiric evidence from a management trial of prompt endoscopy in older patients that this is the strategy of first choice. Delaney *et al.* evaluated the cost-effectiveness of an initial endoscopy compared with usual management in patients with dyspepsia over the age of 50 presenting in primary care.[67] A total of 422 patients were randomly assigned to either usual care or initial endoscopy; the initial endoscopy arm showed significant improvement in symptom scores and quality of life as well as a 48% reduction in the use of PPIs. Hence, initial endoscopy in older patients with dyspepsia at least in thisU.K. studywas potentially cost-effective provided the cost of EGDwas low. The cost effectiveness of endoscopy in older people in the U.S. setting needs investigation.

There is only limited and unconvincing evidence that endoscopy leads to improved patient satisfaction scores in dyspepsia. Bytzer *el al.* conducted a randomized trial comparing prompt endoscopy with empiric H2-receptive blocker therapy in dyspepsia.[68] They found there was significant improvement in satisfaction scores at one month after endoscopy compared to the empiric antisecretory therapy arm. In addition, 66% of the patients in the empiric therapy arm eventually underwent endoscopy during the 12 months of follow-up. However, this unblinded study may have been biased by patient and physician expectation that endoscopy is the preferred management strategy, and *H. pylori* status was not considered.

Other studies have suggested that patients with dyspepsia are reassured by EGD and may require fewer prescriptions, although the duration of reassurance is not established.[69-71]

Dyspeptic patients who seek medical attention are more concerned about the possible seriousness of their symptoms and are more likely to be concerned about underlying cancer.Health anxiety has been shown to lead to a cycle of repeated medical consultations. In a study of primary care patients undergoing open-access endoscopy, Hungin *et al.* demonstrated that consultations for dyspepsia fell by 57% in patients with normal endoscopy and by 37% in patients with minor

abnormalities at endoscopy. In 60% of patients with normal endoscopy, medication use was terminated or decreased.[72] Quadri and Vakil demonstrated that one third of patients referred for open-access endoscopy for dyspepsia in the United States had high levels of health related anxiety; following a normal endoscopy or the demonstration of minor abnormalities, and reassurance by the endoscopist, scales for preoccupation with health and fear of illness and death showed significant improvement after endoscopy, and the effects were preserved for 6 months.[73]

Disadvantages of Endoscopy

There are several potential disadvantages of prompt endoscopy for all dyspeptic patients that need to be carefully considered. Endoscopy is invasive and although the risks of this procedure in relatively healthy patients are very low, the issue of the risk-benefit ratio needs careful weighing, particularly as the procedure is very unlikely to identify an unexpected structural cause in a young patient with no alarm features. Finding esophagitis, the most likely structural abnormality, may often not lead to a change in management.[74,75] Moreover, the high prevalence of dyspepsia means that a general recommendation to perform endoscopies on all patients would be very costly and would overwhelm endoscopy services. Furthermore, it is contentious that prompt EGD provides any direct benefits despite some positive studies quoted above. One study evaluated management strategies in 326 primary care patients with dyspepsia; endoscopy was not superior to any of the empirical treatment strategies utilized in this study.[76]

A systematic review concluded that most data failed to support the view that endoscopy alone improves patient outcome in dyspepsia compared with other

empiric strategies.[77]

EMPIRIC ANTISECRETORY THERAPY IN UNINVESTIGATED DYSPEPSIA

The American College of Physicians in 1985 recommended an empiric trial of an H2 receptor antagonist for 6–8 wk; those who relapsed after therapy or those who failed

to respond to therapy in 7–10 days were to be referred for endoscopy.

The widespread availability of PPIs has resulted in this class of agents frequently being prescribed as initial empiric therapy in uninvestigated dyspepsia in place of H2 receptor antagonists.[78]

A meta-analysis of several large studies has demonstrated a short course of PPI therapy compared with a H2-receptor antagonist, alginate, or placebo in primary care provides better symptomatic outcomes.[79] However, these studies frequently included patients with symptomatic reflux disease and did not exclude peptic ulcer.

It is unknown whether GERD or ulcer disease, or both, accounts for the apparent short-term benefits of empiric therapy in these reports.

There are limited data that prokinetic therapy employed as an empiric strategy may be efficacious in uninvestigated dyspepsia. Kearney *et al.* noted no significant difference in the severity of dyspeptic symptoms among 60 patients randomized to receive cisapride as compared to placebo in the setting of uninvestigated dyspepsia and negative *H. pylori*-serology.[80]

Quartero *et al.* conducted a trial in primary care of 563 patients who were randomized to ranitidine or cisapride; treatment success was similar in both groups but was under 50%, and the relapse-free periods were also similar with both drugs.[81]

A randomized trial in *H. pylori*-negative dyspepsia from Canada demonstrated that cisapride had low efficacy and was inferior to acid suppression.[82] Moreover, cisapride is no longer available because of rare toxicity from QTC prolongation and sudden death. There have been no trials of metoclopramide, tegaserod or domperidone in the management of uninvestigated dyspepsia.

Obvious disadvantages of empiric antisecretory therapy include the concern that peptic ulcer disease will be inappropriately and inadequately treated, and patients subsequently may present with complicated ulcer disease if for any reason the therapy is ceased.

Antisecretory therapy can also lead to misdiagnosis of peptic ulcer disease at subsequent endoscopy, as the ulcer will more likely heal and be missed. The impact of acid rebound in dyspepsia remains unclear. Empiric antisecretory therapy may lead to long-term inappropriate maintenance therapy that

the patient does not require.

It is unclear whether antisecretory therapy postpones eventual investigation or not, which in turn impacts on its potential cost-effectiveness.

H.pylori TEST-AND-TREAT *VERSUS* EMPIRIC ANTISECRETORY THERAPY

There are only very limited data comparing empiric *H. pylori* treatment *versus* empiric PPI therapy.

Manes *et al*[83] compared test-and-treat with PPI therapy for a month with 12 months of follow-up in a secondary care setting in Italy. In the test-and-treat arm, 56% were eventually endoscoped because of poor symptom control, but none had a peptic ulcer; in the PPI arm, 88% were endoscoped and 17% had a peptic ulcer, but most (88%) were infected with *H. pylori*.

More studies are needed, but these data suggest that in *H. pylori* positive dyspeptic patients, empiric PPI therapy is not the management option of choice in areas where the prevalence of *H. pylori* is high

ACG 2005[11] :

In H. pylori-negative cases with uninvestigated dyspepsia and no alarm features, an empiric trial of acid suppression for 4–8 wk is recommended first-line therapy (Grade of evidence: A)

If initial acid suppression fails after 2–4 wk, it is reasonable to step up therapy, although this is based on expert opinion only; this may require changing drug class or dosing. In the absence of established prokinetic drugs for dyspepsia in the United States, this drug class is not currentlyrecommended as first-line therapy for dyspepsia inthe United States.(Grade of evidence: C)

In patients who do respond to initial therapy, it is recommended that treatment be stopped after 4–8 wk and if symptoms recur, another course of the same treatment is justified.There are no data on long-term self-directed therapy in this condition, although this may be worth considering in some patients.(Grade of evidence: C)

MANAGEMENT OF DOCUMENTED FUNCTIONAL DYSPEPSIA

Once a diagnosis of functional dyspepsia is confirmed by a negative endoscopy, an empiric trial of therapy is commonly prescribed. However, the benefits of all therapies in this condition have been questioned. Many patients do not require medication for dyspepsia after they have had reassurance and education. It is therefore important for the clinician to explain the meaning ofthe symptoms and their benign nature.

Ascertaining why a patient with long-standing symptoms has presented on this occasion for care can be helpful, as this may identify those who have fears of an underlying serious disease or specific psychological distress that can be addressed. Potential precipitating factors in dyspepsia remain poorly defined. High-fat meals should be avoided; eating frequent and smaller meals throughout the day can sometimes be helpful. Specific foods that precipitate symptoms can be avoided. Food intolerance is uncommon, however, and food allergy very rare. Follow-up of the patient helps determine the natural history and allows further correction of faulty ideas and provides reassurance that can be very helpful in long-term management.

Antacids and sucralfate were not superior to placebo in functional dyspepsia based on a Cochrane review.[78] However,a recent trial of simethicone has suggested potential benefit compared with placebo, and in another study equivalence with cisapride.[84]

A Cochrane review of 8 trials of H2 receptor antagonists with 1,125 patients showed a relative risk reduction of 30% but the quality of the trials was generally poor . PPIs in this review also produced a relative risk reduction of approximately 30% and the quality of the trials was better.[78]

An economic model suggested that PPI therapy was cost-effective for functional dyspepsia in the United States.[85] However, in a recent randomized trial of 453 patients from Hong Kong, the proportion of patients achieving complete relief of dyspepsia with lansoprazole 30 and 60 mg was 23% and 23%, respectively, compared with 30% on placebo.[86]

In contrast, another recent trial reported significant benefit with lansoprazole in a U.S.

population.[87] *H. pylori* status is unlikely to affect the therapeutic outcome of acid suppression therapy in functional dyspepsia. Large trials have failed to identify any difference in therapeutic outcome in *H. pylori*-positive *versus* negative patients, although Blum *et al.* did identify a superior response to PPI therapy in *H. pylori*-positive patients.[88]

Eradication of *H. pylori* in functional dyspepsia is controversial. Two high-quality meta-analyses have reached different conclusions but this may be likely explained by which trials were included and excluded in each systematic review. Updating these meta-analyses now suggests that when all appropriate trials are considered, there is a small but significant therapeutic gain achieved with *H. pylori* eradication in functional dyspepsia, with the number needed to treat being 15. While longer than 1-yr follow-up data are generally lacking, one 5-yr study suggests any benefit will persist .

On the basis of the evidence, it is acceptable to offer *H. pylori* eradication therapy to infected patients with functional dyspepsia. The results also imply that offering *H. pylori* eradication therapy empirically to those with otherwise uninvestigated dyspepsia who are infected is reasonable even if ulcer disease is unlikely. Moreover, *H. pylori* eradication in those with documented functional dyspepsia may help prevent ulcer disease, although convincing evidence is not available.

Hsu *et al.* observed during 1yr of follow-up in a randomized controlled trial comprising 161 patients with functional dyspepsia, 2 patients in the *H. pylori* eradication treatment group (3%) and 6 patients in the placebo group (8%) developed peptic ulcers at repeat endoscopy .

The benefit of other treatments remains uncertain. A Cochrane review included 12 trials with prokinetics comprising 829 patients and showed that there was a relative risk reduction of 50%, compared with placebo, but most of the studies were with cisapride . Moreover, analysis of the studies suggested that publication bias at least partly explains the apparent benefits of prokinetic therapy. Prokinetics should be reserved for difficult cases as options in the United States are few and current

agents (*e.g.*, metoclopramide, erythromycin, tegaserod) have limited or poorly established efficacy,or side-effects are common .

Routine use of gastric emptying studies is not recommended as improvements in gastric emptying do not correlate well with symptom improvement . Drugs that relax the gastric fundus (*e.g.*, tegaserod, cisapride, sumatriptan, buspirone, clonidine, some SSRIs, nitric oxide donors) may theoretically improve some dysmotility-like dyspepsia (*e.g.*, early satiety) but adequate randomized controlled trials are lacking .

Antidepressants are also of uncertain efficacy in functional dyspepsia but are often prescribed. There are insufficient data on the use of tricyclic antidepressants such as amitryptyline in dyspepsia, but small studies have suggested benefit; however,the beneficial effect of low-dose amitryptyline seen in functional dyspepsia was not related to changes in perception of gastric distension . An increased tolerance to aversive visceral sensations may play a role in the therapeutic effect. There are limited data with the SSRIs. Psychological therapies are promising, particularly hypnotherapy, but more data are needed in larger patient populations before these can be recommended for routine use. Other alternative therapies such as herbal preparations remain of unproven value .

ACG 2005 :

The management of endoscopy-proven functional dyspepsia is particularly challenging when initial antisecretory therapy and H. pylori eradication fails. Patients who fail to respond to simple measures need to have their diagnosis reconsidered. Dietary therapy has no established efficacy but may help some individuals. There are very limited data to support the use of herbal preparations, simethicone, and low-dose tricyclic antidepressants in functional dyspepsia. Bismuth, sucralfate, and antispasmodics are not established to be of benefit over placebo in functional dyspepsia. Hypnotherapy, psychotherapy, and cognitive-behavioral therapy are supported by limited studies but

cannot be generally recommended at the present time.

Grades of evidence:

Dietary modification: C

Simethicone: B

ADDITIONAL DIAGNOSES AND TESTING IN REFRACTORY CASES

Abdominal wall pain can be confused with functional dyspepsia; physical examination here is diagnostic (increased rather than reduced tenderness on tensing the abdominal wall muscles). Biliary pain is characteristic and different from dyspepsia; ultrasound usually is unhelpful in the absence of typical biliary pain. Exclusion of atypical GERD with esophageal pH testing may alter management; at least 20% of patients with diagnosed functional dyspepsia clinically turn out to have GERD on esophageal pH studies . Thus, even if a trial of PPI therapy has failed, pH testing may be considered off therapy, although the yield in this particular setting is not defined. Abdominal imaging to rule out chronic pancreatitis or small bowel pathology may be worth considering too but usually has a low yield; capsule endoscopy does not yet have an established role here. Gastric function testing (gastric emptying; gastric accommodation; response to a nutrient or water load) may not change management even if abnormalities are detected, although, if there is gastric dysaccomodation, trials of various drugs to relax the fundus may be worth trying empirically .

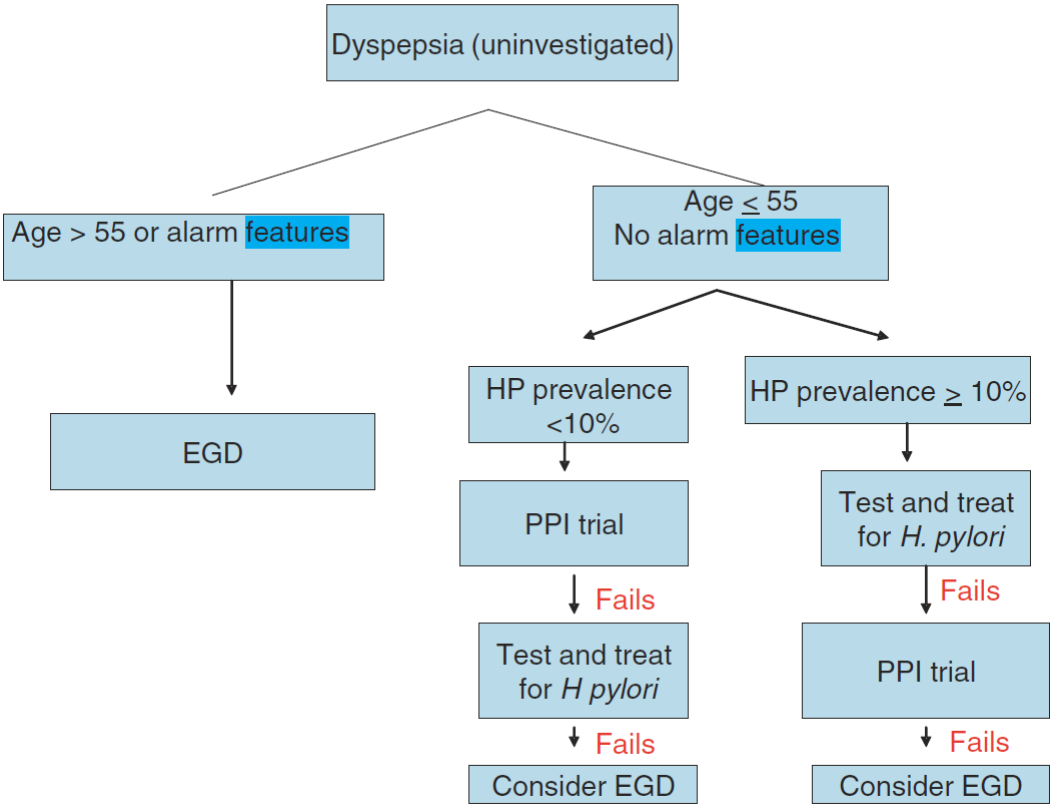
Questions about symptoms consistent with IBS may lead to a change in the diagnosis. Colonic evaluation may be considered even if there are no bowel disturbances because disease in the transverse colon or elsewhere can occasionally present with referred symptoms labeled dyspepsia.

A drug history is helpful but aside from NSAIDs, drugs are rarely major contributors

to chronic dyspepsia according to the available evidence . Diabetic radiculopathy can cause upper abdominal pain and EMG is diagnostic. Evaluation for referred pain from the chest or back should be considered in difficult cases.

Finally, consider looking for rare metabolic or other causes of upper abdominal pain including thyroid disease, electrolyte abnormalities, hypercalcemia, heavy metals, acute intermittent porphyria, angioneurotic edema, familial mediterranean fever, chronic intestinal angina, superior mesenteric artery syndrome, liver disease (hepatoma, steatohepatitis), eosinophilic gastroenteritis, or connective tissue disease.

Algorithm for the management of Univestigated dyspepsia



MATERIALS AND METHODS

All patients who attended the Gastroenterology Outpatient clinic of the Stanley Medical College Hospital between October 2008 and March 2009 with features of dyspepsia were enrolled.Those patients with alarm features were included in the study.

Alarm features defined in the study were dysphagia,persistent vomiting,early satiety, anemia,anorexia,unintended weight loss,Upper Gastrointestinal bleed,,abdominal mass, lymphadenopathy, jaundice, High risk features(family history of GI cancer,previous history of gastric surgery). Those dyspeptic patients above 45 years of agewithout alarm features were also included for endoscopic evaluation as per the recommendation. Patients with prior NSAID use,known diabetics,medical comorbidities,known gastric/esophageal cancer were excluded.

At their first visit,data was collected in a structured proforma (Annexure I) incorporating the upper abdominal symptom questionnaire and were given a full diagnostic workup,as considered appropriate based on the presenting symptoms.

The data included age, gender, educational status, income, family members, dyspeptic symptoms, alarm symptoms with their duration,relevant findings on physical examination,basiclaboratorydata(Hemogram,Bloodsugar,Bloodurea,Serumcreatinine),Imaging(X ray chest,Ultrasound abdomen,CT abdomen) and findings at UGI endoscopy.Questionnaire data were collected prospectively in the above mentioned time period. Data were then retrospectively analysed.Ethics committee approval was obtained prior to initiaton of the study

STATISTICAL ANALYSIS

Prevalence estimates were done for all alarm features,age and gender related factors,without ,alarm features,enodoscopy outcomes.Univariate analysis were assessed using Pearson's χ^2 test; some factors done with chi square test(Fisher's exact probability test).Comparisons were performed between positive endoscopy outcomes with all independent variables.

Multivariate analysis was done with multiple linear logistic regression model.Significant alarm features which were identified with univariate analysis were entered into a regression model and backward stepwise elimination was used to identify the best subset of factors that predicted the positive endoscopy outcome.i.e gastro esophageal malignancy.Odds ratio with 95% confidence intervals were recorded for all significant factors identified in univariate and multivariate analysis.P value of < 0.05 was considered significant.

RESULTS

A total of 1984 patients with symptoms of dyspepsia presented to the Gastroenterology Outpatient service during the study period. 283 patients satisfied the inclusion criteria and were enrolled in the study.

2 patients did not turn up for the Upper Gastrointestinal Endoscopy procedure.

2 patients had incomplete study as they were not cooperative during the endoscopy procedure.

In total,279 patients who underwent endoscopy successfully entered the study.

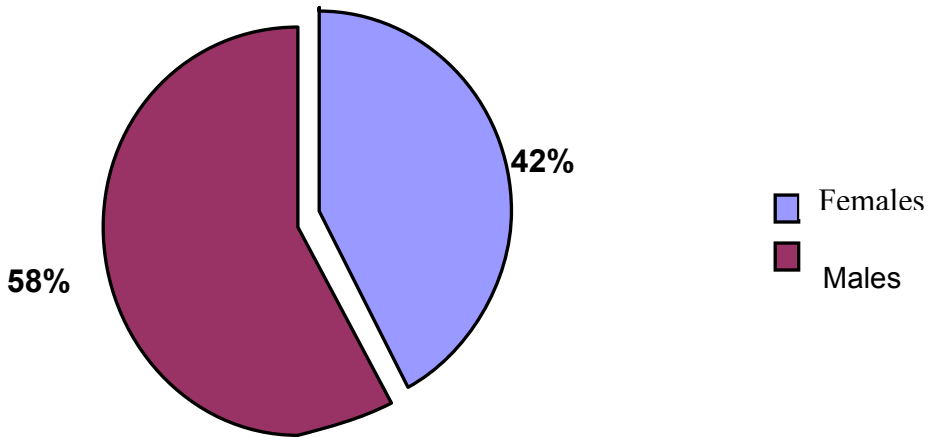
There were 162(58.1%) males and 117 (41.9%) females.

Mean patient age was 50.73± 13.88 and no gender difference observed

(Males Vs Females = 51.06 ± 14.24 Vs 50.27 ± 13.43,p=0.64).

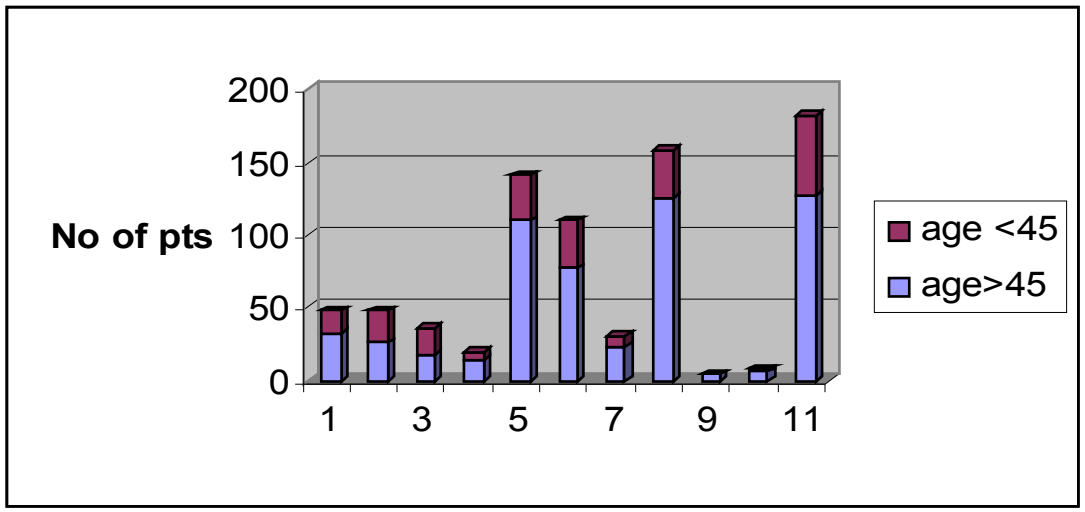
205 patients (73.5%) were above 45 years of Age.

Fig 1. Gender prevalence



Anorexia,weight loss,anemia were the common alarm features noted overall.In the younger age group i.e < 45 years ,the common alarm features were weight loss(11.8%) and anemia(11.8%).Whereas in age>45years, anemia was the commonest(44.8%). Combination of alarm features present in 65.2% of patients.Anemia was more prevalent in both gender.

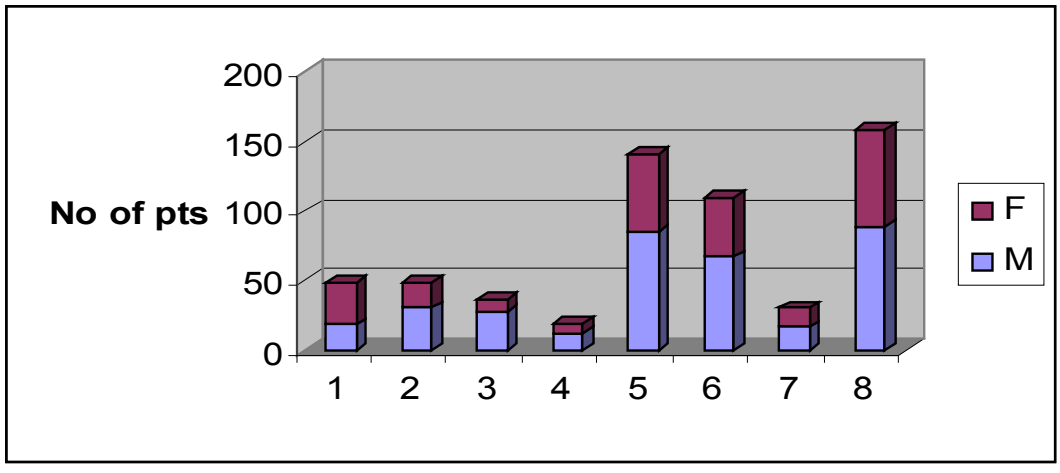
Fig 2. Prevalence of individual alarm features in relation to age group



(1-dysphagia,2-persistent vomiting,3-early satiety,4-Upper GI bleed,5-anorexia, 6-wt loss,

7-easy fatiguability,8-anemia,9-mass abdomen,10-high risk features, 11-alarm combination)

Fig 3. Prevalence of alarm features – gender related



Prevalence of alarm features in relation to Age ,Gender:

Table 1.Gender Vs Alarm

	Alarm present	Alarm absent
Males	145	17
females	97	20
Total	242	37

(p = 0.1)

Table 2. Age group Vs Alarm

	Alarm present	Alarm absent
Age > 45 years	168	36
Age < 45 years	75	0
Total	243	36

(p< 0.001)

Table 3. Gender Vs Alarm in Age > 45 years

	Alarm present	Alarm absent
Males	101	17
Females	67	19
Total	168	36

(p = 0.2)

There was no significant difference in the prevalence of alarm features with respect to Gender overall.

Alarm features were more prevalent in older age groups(age > 45 years) compared to younger age group(statistically significant p<0.001).

In the age group > 45 years , there was no significant difference in the prevalence of alarm with respect to gender.

Table 4. Gender Vs alarm combination

	Alarm combination present	Alarm combination absent
Males	112	50
Females	70	47
Total	182	97

(p = 0.1)

No significant difference in gender noted with respect to prevalence of alarm combination.

Malignancy outcomes :

Of the 279 patients who underwent endoscopy,38 patients**(13.6%)** were diagnosed to have malignancy (proven histologically).17 presented with esophageal malignancy, 18 with gastric malignancy, 2 with GE Junction malignancy and 1 patient with periampullary malignancy.

Benign lesions were found in 160 patients(57.3%): DU (15.6%), gastric ulcer (GU) (7.1%), gastric erosions(9.1%),oesophagitis (6.8%), gastritis (10.2%) and duodenitis (13.6%).Normal study found in 81 patients(29.1%).

Table.5 Age distribution of Upper GI malignancies

	Total number of patients	< 45 years	45 – 60 years	> 60 years
Total number of pts with upper GI malignancies	38	4(10.5%)	19(50%)	15(39.5%)
Pts with alarm features	37(97.4%)	4(10.5%)	18(47.4%)	15(39.5%)
Pts without alarm features	1(2.6%)	0	1(2.6%)	0

About 89.5% of patients with Upper GI malignancy was found in the age

group > 45 years. 86.9% of these patients presented with alarm.Only 1 patient (2.6%) presented without alarm.

In the younger age group all patients (100%) presented with alarm**.**

Table.6 Gender distribution of Upper GI malignancies

	Total number of patients	Males	Females
Total number of pts with upper GI malignancies	38	25(65.8%)	13(34.2%)
Pts with alarm features	37(97.4%)	25(65.8%)	12(31.6%)
Pts without alarm features	1(2.6%)	0	1(2.6%)

65.8% of males with Upper GI malignancy presented with alarm whereas 31.6% of females presented with alarm.

TableNo7.Age group with alarm Vs malignancy

	Malignancy positive	Malignancy negative
Age > 45 yrs	33	135
Age< 45 yrs	4	70
Total	37	205

(p = 0.008)

Prevalence of malignancy was significantly associated with older age group patients (>45 years) with alarm features(p=0.008) compared to younger age group with alarm.

Table 8. Gender Vs malignancy outcome among patients > 45 years

	Malignancy positive	Malignancy negative
Males	22	79

Females	11	56
Total	33	135

P=0.43

Among the patients of above 45 years,there was no significant difference between males and females in relation to malignant outcomes.

Table 9. Significance of individual alarm features & alarm combination in the diagnosis of Upper GI malignancy

S.No	Variables		Malignancy positive	Malignancy negative	P value	Odds Ratio(95%CI)
1.	**Age**	**>45 yrs**	**34**	**170**	**0.01**	**3.55(1.21-10.37)**
		<45 yrs	**4**	**71**		
2.	Sex	Males	25	137	0.3	-
		Females	13	104		
3.	**Dysphagia**	**Yes**	**16**	**32**	**<0.0001**	**4.75(2.25-9.99)**
		No	**22**	**209**		
4.	**Vomiting**	**Yes**	**13**	**35**	**<0.003**	**3.06(1.43-6.54)**
		No	**25**	**206**		
5.	UGI Bleed	Yes	4	32	0.8*	-
		No	34	209		
6.	**Early satiety**	**Yes**	**8**	**11**	**0.01***	**5.57(2.07-14.96)**
		No	**30**	**230**		
7.	**Anorexia**	**Yes**	**28**	**113**	**0.002**	**3.17(1.47-6.81)**
		No	**10**	**128**		
8.	**Weight loss**	**Yes**	**31**	**79**	**0.0001**	**9.08(3.83-21.52)**
		No	**7**	**162**		
9.	**Easy fatiguability**	**Yes**	**12**	**18**	**0.0001***	**5.71(2.47-13.18)**
		No	**26**	**223**		
10.	**Anemia**	**Yes**	**36**	**122**	**<0.0001**	**17.55(4.13-74.55)**
		No	**2**	**119**		
11.	**Mass abdomen**	**Yes**	**3**	**1**	**0.008***	**20.57(2.08-200.3)**
		No	**35**	**240**		
12.	High risk features	Yes	O	8	0.4	-
		No	38	233		
13.	**Alarm combination**	**Yes**	**13**	**39**	**0.008**	**2.69(1.26-5.71)**
		No	**25**	**202**		

Statistically significant variables on Univariate analysis were Age>45 yrs(p=0.01), dysphagia(p<0.0001)vomiting(p<0.003),earlysatiety(p=0.01),anorexia(p=0.002), weightloss(p<0.0001),easyfatiguability(p=0.0001),anemia(p<0.0001), mass abdomen(p=0.008) and alarm combination(p<0.001). Alarm features like Upper Gastrointestinal bleed,High risk features and gender were not statistically significant to diagnose or to predict Upper GI malignancy.

Table 10. Duration of symptoms and outcome of endoscopy

S.No	**Alarm duration**	**Outcome(%)**		**X^2 test**	**P value**
		Malignancy positive	**Malignancy Negative**		
				32.1	**<0.0001(df=3)**
1.	≤ 3 months	33	61		
2.	4 – 6 months	2	20		
3.	7 – 9 months	1	24		
4.	> 9 months	0	48		

The above table shows an inverse correlation of positive outcomes of endoscopy i.e malignancy positive with the duration of alarm symptoms.This is is statistically significant(p<0.0001).

Table.11 Multivariate analysis using multiple linear logistic regression model with backward elimination

S.No	Variables	P value	Odds ratio	95%CI
1.	**Age > 45 years**	**0.02**	**4.27**	**1.18 – 15.3**
2.	**Dysphagia**	**0.003**	**4.3**	**1.6 – 11.7**
3.	**Vomiting**	**0.02**	**3.36**	**1.18 – 9.51**
4.	Early satiety	0.2	-	-
5.	anorexia	0.1	-	-
6.	**Weight loss**	**0.008**	**6.2**	**1.6 – 24.4**
7.	Easy fatiguability	0.13	-	-
8.	**Anemia**	**0.01**	**9.1**	**1.6 – 50.5**
9.	Mass abdomen	0.6	-	-
10.	Alarm combination	0.3	-	-

The 10 variables which showed significant values bu Univariate analysis were entered in multivariate analysis.5 of the 10 variables emerged statistically significant after multivariate analysis using Multiple linear logistic regression model.

They were Age > 45 years(p=0.02), Dysphagia(p=0.003), Vomiting(p=0.02),

Weight loss(p=0.008) and Anemia (p=0.01).

DISCUSSION

It is well recognised that clinical history is a poor guide to the underlying diagnosis of dyspepsia. Approximately 3–4% of the population consult their general practitioner with Upper intestinal symptoms each year, of which over 10% will have so-called alarm symptoms.It is important to identify the malignancy in patients presenting with dyspepsia.The set guidelines by the Western world may help in picking up the lesion. Unfortunately malignancies were picked up late in their presentation by the alarm symptoms and no standard guidelines established for the Indian population.

Also not all the alarm features mandate an immediate endoscopy.Eventhough the cost of endoscopy is low in India compared to Western world,it may result in overburden of the working staff,wasting of manpowerand resources.

The present study highlighted that dysphagia, age>45years, persistent vomiting, anemia and weight loss were the alarm features in dyspeptic patients which predicted significantly the malignant outcomes. Kapoor et al[48] in his study identified dysphagia (odds ratio (OR) 3.1 (95% confidence interval (CI) 1.80–5.22)), weight loss (OR 2.6 (95% CI 1.53–4.41))and age >55 years to be the significant positive predictive factors for cancer.This is similar to the present study except for the age group and alarm features like anemia,vomiting.

Age is an important criterion (even without alarm features) while screening patients with dyspepsia for cancer. Among the Western population, the incidence of oesophageal and gastric cancers is very low for patients below the age of 45 years, and the Western recommendations do not justify the use of endoscopy in these patients to detect early cancer.The incidence of gastroesophageal cancers in Indian population is high and the age of onset ,presentation were early.Sumathi et al[45] in her recent study highlighted that even taking the age cut-off as 45 years for diagnostic endoscopy, 18.3% of malignancies were missed.The study arrived an age cut – off (males -43.5 years,females - 38

years).The present study eventhough taken the age cut-off as 45years(as per ACG 1985 guidelines) , it was found to be the single most diagnostic predictor for malignancy.This again signifies that age cut – off for the Indian population should be separately assigned by prospective controlled studies in future and not to follow the age age > 55years as an alarm feature to proceed with endoscopy(ACG 2005).

The Prevalence of alarm features were more commonly seen in dyspeptic patients in older age group. Sundar et a[50] in his retrospective study found that alarm features were present more significantly in age > 45.The present study also showed a significant difference in the prevalence of alarm features ($p < 0.001$) between the younger and older age groups.Also the presence of alarm in older age group was significantly associated with positive malignancy outcomes in patients with dyspepsia. The present study showed that alarm features in age > 45 years predict more significantly($p = 0.008$) the malignant outcomes than younger age group with alarm.

The prevalence rates of gastresophageal cancer vary.Depending on them,the factors which predict cancer may also vary.Kapoor et al showed a prevalence rate of 3.8% in his study. The present study found the prevalence to be 13.6%.

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Summary and Conclusions

The alarm features like dysphagia(p=0.003), persistent vomiting(p=0.02), anemia(p=0.01), age>45 years(p = 0.02) and weight loss(p = 0.008) were identified as significant predictors for Gastroesophageal malignancy in dyspeptic patients.

No gender difference observed to influence the malignant outcome(p = 0.3).

The duration of alarm inversely correlates with malignant outcome(p<0.0001).

Presence of alarm combination do not significantly increase the chances of malignancy (p=0.3)

Alarm features in age > 45 years predict more significantly(p=0.008) the malignant outcomes than younger age group with alarm.

Alarm features like Upper GI bleed(p=0.8), early satiety(p=0.2), anorexia(p=0.1), easy fatiguability(p=0.13), mass abdomen(p=0.6) do not predict significantly Gastroesophageal malignancy.

Based on the results of the present study,we recommend the following guidelines that can be followed in our set up:

1.Irrespective of age group, any dyspeptic patient with alarm should be subjected to Upper GI endoscopy to rule out malignancy as per the recommendation.But the urgency of endoscopy can be prioritised.

(a) In Age > 45 years presenting with alarm,Upper GI endoscopy should be done urgently/at the earliest without even waiting for the baseline investigations.

(b) In Age > 45 years without alarm & younger patients with alarm,Upper GI scopy can be done in an elective basis or after undergoing baseline investigations.

2.Patients presenting with dysphagia,vomiting ,weight loss,anemia should be done endoscopy in an urgent basisThe above indications may minimize the workload to the endoscopist and at the same time identifies the malignancy at the earliest.

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ANNEXURE I

Predictors of positive endoscopic findings in Dyspeptic patients with alarm features

Name : Age/Sex : MGE No :

Occupation : Education : DOR :
Address :

Marital status : No of children : No of family members :
Net family income : Religion :
Veg/Non veg :
Clinical diagnosis :

S.No	Clinical parameters	Duration/Details	S.No	Clinical examination	Status/details
1	Dysphagia		1	Anemia	
2	Hold up throat		2	Jaundice	
3	Odynophagia		3	Clubbing	
4	Heart burn		4	Edema	
5	Retrosternal chest pain		5	Lymphadenopathy	
6	Regurgitation		6	Oral thrush	
7	Epigastric pain		7	Pulse rate	
8	Post prandial epigastric fullness		8	BP	
9	Epigastric discomfort		9	BMI	
10	Abdominal bloating		10	ABDOMEN	
11	Nausea/vomiting			Epigastric tenderness	
12	Early satiety			Epigastric mass	
13	Ball rolling movements			VGP	
14	Hemetemesis			Scar	
15	Melena			Hepatomegaly	
16	Anorexia			Splenomegaly	
17	Weight loss			Others	
18	Mass abdomen		11	Per rectal	
19	Easy fatiguability/exhaustion				
20	jaundice				
21	Abdominal distension				
22	Family history of GI malignancy				
23	H/o previous gastric surgery				

S.no	Investigations	Report

1	Hb	
2	TC	
3	DC	
4	ESR	
5	Platelet count	
6	Peripheral smear	
7	B.Sugar	
8	B.urea./S.Creatinine	
9	LFT	
10	CXR	
11	AXR	

USG Abdomen :

CECT(thorax/abdomen) :

UGI SCOPY :

Biopsy report :